

REC'D 12 JAN 2005

WIPO

PCT

Europäisches
Patentamt

European
Patent Office

Office européen
des brevets



IB/2004/052862

Bescheinigung

Certificate

Attestation

Die angehefteten Unterlagen stimmen mit der ursprünglich eingereichten Fassung der auf dem nächsten Blatt bezeichneten europäischen Patentanmeldung überein.

The attached documents are exact copies of the European patent application described on the following page, as originally filed.

Les documents fixés à cette attestation sont conformes à la version initialement déposée de la demande de brevet européen spécifiée à la page suivante.

Patentanmeldung Nr. Patent application No. Demande de brevet n°

03104918.2 ✓

**PRIORITY
DOCUMENT**
SUBMITTED OR TRANSMITTED IN
COMPLIANCE WITH RULE 17.1(a) OR (

Der Präsident des Europäischen Patentamts;
Im Auftrag

For the President of the European Patent Office

Le Président de l'Office européen des brevets
p.o.

R C van Dijk

BEST AVAILABLE COPY



Europäisches
Patentamt

European
Patent Office

Office européen
des brevets

Anmeldung Nr:

Application no.: 03104918.2 ✓

Demande no:

Anmeldetag:

Date of filing: 22.12.03 ✓

Date de dépôt:

Anmelder/Applicant(s)/Demandeur(s):

Koninklijke Philips Electronics N.V.
Groenewoudseweg 1
5621 BA Eindhoven
PAYS-BAS

Bezeichnung der Erfindung/Title of the invention/Titre de l'invention:

(Falls die Bezeichnung der Erfindung nicht angegeben ist, siehe Beschreibung.

If no title is shown please refer to the description.

Si aucun titre n'est indiqué se référer à la description.)

Apparatus and method for performing orthogonal polarized spectral imaging (OPSI)

In Anspruch genommene Priorität(en) / Priority(ies) claimed /Priorité(s)
revendiquée(s)

Staat/Tag/Aktenzeichen/State/Date/File no./Pays/Date/Numéro de dépôt:

Internationale Patentklassifikation/International Patent Classification/
Classification internationale des brevets:

A61B5/00

Am Anmeldetag benannte Vertragsstaaten/Contracting states designated at date of
filing/Etats contractants désignées lors du dépôt:

AT BE BG CH CY CZ DE DK EE ES FI FR GB GR HU IE IT LU MC NL
PT RO SE SI SK TR LI

Apparatus and method for performing orthogonal polarized spectral imaging (OPSI)

The present invention relates to a method and system for detection of objects below the surface of diffuse scattering media, and in particular blood capillaries, in organs, such as the skin of human beings, using Orthogonal Polarized Spectral Imaging (OPSI), as described by the preamble of independent patent claim 1.

5

It is a well know tendency in all areas of medical care, to provide methods and systems that allow for a minimally or non-invasive treatment of patients amongst others to reduce both risks, and stress for the patient. In line with this tendency, projects have been created to provide methods of non-invasive blood analysis. In the Non-Invasive Blood Analysis one of the possibilities is to measure the concentration of various analytes in blood in vivo by means of confocal Raman spectroscopy.

To achieve a Raman signal from blood instead of skin, the blood capillaries near the skin surface have to be visualized and the Raman detection volume has to be aimed at one of these capillaries. Blood capillaries close to the skin surface have a diameter of 5 to 15 μm . Due to confocal detection; the source of the collected Raman signal is well confined in all three dimensions in a spot of $<5 \times 5 \times 10 \mu\text{m}^3$. This allows collecting a Raman signal from blood without a background signal from skin tissue if the focus is located in a blood capillary.

In this respect, a simple, cheap, and robust method to visualize blood vessels close to the surface of organs is the Orthogonal polarized spectral imaging (OPSI). Medical applications of Orthogonal Polarization Spectral Imaging can for example be taken from WO 01/22741, which is incorporated by reference herein. In a recent test it was shown that it is also possible to use OPSI to visualize blood capillaries in the human skin. In OPSI polarized light is incident on the skin through a polarizing beam splitter. Part of the light reflects directly from the surface (specular reflection). Another part penetrates into the skin where it scatters one or more times before it is absorbed or is re-emitted from the skin surface (diffuse reflection). In any of these scattering events there is a chance that the polarization of the incident light is changed. Light that is directly reflected or penetrates only slightly into the

skin will scatter only one or a few times before it is re-emitted, and will mostly retain its initial polarization. On the other hand, light that penetrates more deeply into the skin undergoes multiple scattering events and is depolarized before re-emitted back towards the surface. When looking at the subject through a second polarizer, oriented precisely

5 orthogonal to that of the first polarizer, light reflected from the surface or the upper parts of the skin is largely suppressed, whereas light that has penetrated deeper into the skin is mostly detected. As a result the image looks as if it were back-illuminated. Because wavelengths below 590 nm are strongly absorbed by blood, the blood vessels appear dark in the OPSI image, though.

10 The reliability of a measured concentration of analytes in blood directly depends on the ability to direct the Raman detection volume inside a blood vessel. However, even though Orthogonal polarized spectral imaging (OPSI) is a method to detect blood capillaries in human skin, it is essentially a 2-dimensional technique, whereas a
15 3-dimensional image would be desirable to be able to exactly aim the Raman detection volume. While the lateral resolution of OPSI is of the same order of magnitude as the Raman technique, OPSI hardly provides any depth information. The only depth discrimination available is caused by the depth of focus of the imaging objective. As the capillary moves out of the focal plane, it is blurred. Using the sharpness of the imaged blood vessels to determine the depth of the vessels has several disadvantages: it is not very precise; when the capillary is
20 seen as blurred it is not a priori clear if the capillary is above or below the focal plane; when the capillary is seen as blurred it is not a priori clear what the distance is between the blood capillary and the focal plane. An additional complication is that even in-focus images of blood capillaries are blurred because of light scattering in the skin tissue above the blood capillary. The lack of reliable depth information makes it difficult to aim the Raman laser at a
25 blood vessel.

Accordingly, it is an object of the present invention to provide a method and system for detection of objects below the surface of diffuse scattering media, and in
30 particular blood capillaries, in organs, such as the skin of human beings, using Orthogonal Polarized Spectral Imaging (OPSI), which allows a more precise localization of the objects, and in particular capillaries in the human skin.

This object is solved by the features according to the independent claims, wherein the features as contained in the dependent claims describe preferred, and useful embodiments.

5 Provided is a method for detection of objects below the surface of diffuse scattering media, and in particular blood capillaries in organs, such as the skin of human beings, using Orthogonal Polarized Spectral Imaging (OPSI), according to the invention comprising the steps of, imaging the object in question under at least two different angles, to obtain a shift of position in the imaging plane; and subsequently comparing relative shifts of objects in the two images to obtain coordinates of the imaged objects with respect to the focal
10 plane.

Accordingly, it is proposed to use a stereoscopic variety of OPSI to obtain depth information, wherein the blood capillaries are imaged under different angles, resulting in a shift of position in the image plane. From direction of the shift it can be determined if the blood capillary is above or below the focal plane, whereas the distance between the blood
15 capillary and the focal plane can be calculated from the size of the shift. Stereoscopy is a well-known technique for conventional microscopy. The object is imaged under different angles and depth information is obtained by comparing relative shifts of objects in the two images. The human brain does this automatically when the eyes separately view the two images. Image analysis algorithms are also able to extract this information and quantify it.

20 Modern stereomicroscopes are based on two different concepts. In the so-called Greenough design two identical objectives are used under different angles. In the so-called telescopic design or common objective design, two partial microscope systems are arranged in parallel with each other and use the same main objective. In a preferred embodiment of the invention the angle between the light paths of the at least two images is
25 chosen to be between 10 and 30 degrees.

Furthermore, for non-invasive blood analysis using confocal Raman spectroscopy, a relatively high magnification and high numerical aperture (NA) objective with a short working distance to focus the Raman laser and to collect the Raman signal is used. For ease of construction and alignment and because of space and cost limitations it is
30 advantageous to use the same objective for OPSI. There are basically two ways to obtain a stereoscopic image using a single objective: illuminating only a part of the objective with a parallel beam or illuminating the whole objective under a certain angle.

In OPSI light with a wavelength of 540 to 580 nm is used for detecting blood vessels in human skin. For OPSI imaging a lateral resolution of 1 μm is preferable, which can

be achieved by using a NA of 0.35. The relation between the depth resolution Δz and the stereoscopic angle α is given by

$$\tan \alpha = 0,5 \Delta x / \Delta z.$$

5

Where Δx is the lateral resolution of the system. The factor 0.5 arises because imaging from the left ($-\alpha$) and from the right ($+\alpha$) are compared. Some typical values are given in the table below:

Depth resolution (μm)	Stereoscopic angle (degrees)
1	27
2	14
5	6

10

For a NA = 0.9 objective the maximum angle at which light can travel in object space is 64° . For a lateral resolution of $1 \mu\text{m}$, an effective NA of 0.35 an angle of 21° is required. Therefore, the maximum stereoscopic angle (neglecting other limitations like geometric constraints in image space) is 43° . For this angle the highest depth resolution of $0.54 \mu\text{m}$ is achieved.

15

Furthermore, an apparatus for stereoscopic Orthogonal Polarized Scattering Imaging (OPSI) is provided, for imaging objects below the surface of diffuse scattering media, and in particular blood capillaries, in organs, such as the skin of human beings, comprising at least a light source providing polarized light, an imaging device such as a CCD-camera, a beam splitter, which preferably is a polarized beam splitter, a focusing device such as an objective, or a mirror, and means for imaging the object in two different imaging angles, subsequently or at the same time. The light source preferably is arranged to illuminate a diffuse scattering medium, which upon this illumination illuminates the object with depolarized light. The means for imaging the object can be formed by two objectives having different imaging angles, or by a single main objective, and a scanning mirror for shifting the imaging beam on its path from the polarizing beam splitter to the imaging device. The two imaging angles preferably differ by 10 to 30 degrees.

20

25

Furthermore, separate imaging devices can be provided for each image, or, as an alternative, a shutter for alternating transmission of one of the two images is provided,

which is preferably located between the polarizing beam splitter and the imaging device, and can be embodied as a rotating aperture shutter, a liquid crystal cell shutter, or any other suitable means. The imaging device can for example be a CCD or CMOS camera.

The apparatus can further comprise a data processor for determining a position
5 of the object, wherein the position includes at least information about the z-axis, parallel to the optical axis.

The apparatus may further comprise a spectroscopic analysis system having a spectroscopic light source which may be laser for providing a spectroscopic light beam, a spectroscopic light beam positioning device for directing the spectroscopic light beam to the
10 object in dependence of the position of the object determined by the data processor. The spectroscopic analysis system may be identical to that described in WO 02/057759.

Further features and advantages of the present invention will become more
15 apparent for someone skilled in the art when reading the following description of preferred embodiments in connection with the annexed figures, in which:

Fig. 1 shows a schematic representation of a setup for OPSI;

Fig. 2a shows a schematic representation of the exit pupil of the imaging
objective with OPSI light paths using parallel beams in a top view;

20 Fig. 2b shows a side view of fig. 2a;

Fig. 3 shows an embodiment of the OPSI setup using parallel imaging beams;

Fig. 4 shows an embodiment using the same objective and tilted imaging
beams; and

Fig. 5 shows the schematic position of blood vessels in an image as the
25 function of viewing angle and position relative to the focal plane.

In figure 1 a schematic representation of a typical setup for OPSI is shown, comprising a light source 1, such as a lamp, a laser, an LED, etc., a condenser 2, diaphragm
30 3, a color filter 4, a polarizer 5, a polarizing beam splitter 6, and an objective 7. Furthermore, in Fig. 1 a skin 8 consisting of (a) epidermis, and (b) dermis is shown, together with blood capillaries 9. Finally, an analyzer 10 is shown, wherein polarization is effected perpendicular to polarizer 4, a lens 11, and a CCD camera 12.

In figure 2a the top view of an exit pupil 13 of the imaging objective with OPSI light paths using parallel beams 14, 15 is shown. In a non-invasive blood analyzer an objective with a NA of 0.9 is used. For OPSI imaging a lateral resolution of 1 or 2 μm is required, which can be achieved by using an objective with a NA of 0.35. Because the NA required for OPSI (0.35) is much smaller than the NA available (0.9), it is possible to use only a fraction of the pupil 13 area for imaging. The different stereoscopic angles can be achieved by illuminating different area's of the pupil 13. Using parallel beams 14, 15, the blood vessels 9 in the focal plane are imaged on the same position if observed under both stereoscopic angles. Vessels 9 that lie before or behind the focal plane have a different position in both images. A possible embodiment is shown in figure 3.

The position of the imaging beam in the objective pupil 13 can be shifted by using a scanning (rotating) mirror 16 and a relaying lens 17. If the distance between this lens 17 and the scanning mirror 16 equals the focal distance of the relaying lens 17, a tilt of the mirror 16 results in a parallel displacement of the imaging beam in the objective pupil 13. The distance between the objective pupil 13 and the blood vessel 9 is equal to the focal distance of the objective pupil 13 (corrected for the refractive index of human skin).

An alternative embodiment is shown in figure, 4, whereby the same elements as in the previous figures have been provided with corresponding reference signs. A polarizing beam splitter 6 separates the light paths of the illumination system and the imaging system. The imaging system contains a scanning mirror 16 and a relaying lens 17 such that the pivot point on the scanning mirror 16 is imaged on the center of the objective lens 13. An imaging lens finally is used to image the focal plane of the objective lens 13 onto a CCD camera.

As the scanning mirror 16 performs a wobbling motion, the OPSI image moves. Objects that are in front of or above the focal plane will move less than objects behind or below the focal plane. Objects that are in the focal plane will move over a distance $Mf \tan \beta$, where M is the magnification factor of the OPSI system, f is the focal length of the objective, and β is the viewing angle through the microscope objective. β is related to the scanning angle σ of scanning mirror 16 through $\tan \beta = (A/B) \tan 2 \sigma$, where A is the distance from the scanning mirror 16 to the relaying lens 17 and B is the distance from the relaying lens 17 to the objective lens 13.

Objects that are at a distance δ above the focal plane will move over a distance that is slightly smaller, $M(f - \delta) \tan \beta$, whereas objects at a distance δ below the

focal plane will move over a distance that is slightly larger, $M(f + \delta) \tan \beta$, please refer to figure 5.

In figure 5 the schematic position of blood vessels 18 is shown, The three blood vessels 18a, 18b, 18c shown in figure 5 all overlap in the case of $\beta = 0$, but their
5 projections on the focal plane all have different displacements for $\beta \neq 0$.

Besides the embodiments described above, other embodiments are possible, as for example use of a single imaging device which includes a replacement for the scanning mirror by a rotating wedge, or by two shifting wedges. It is also possible to use 2 imaging devices looking at different angles through the objective. This has the advantage that there
10 are no moving parts and that the images from both sides can be detected simultaneously. From the obtained images, the amount of de-focus can be determined using a correlation function or by subtracting the two images.

Provided is a method and an apparatus for detection of objects below the surface of diffuse scattering media, and in particular blood capillaries, in organs, such as the skin of
15 human beings, using Orthogonal Polarized Spectral Imaging (OPSI), according to the invention comprising the steps of, imaging the object in question under at least two different angles, to obtain a shift of position in the imaging plane; and subsequently comparing relative shifts of objects in the two images to obtain coordinates of the imaged objects with respect to the organ surface.

It should be noted that the above-mentioned embodiments illustrate rather than
20 limit the invention, and that those skilled in the art will be able to design many alternative embodiments without departing from the scope of the appended claims. In the claims, any reference signs placed between parentheses shall not be construed as limiting the claim. The word "comprising" does not exclude the presence of other elements or steps than those listed
25 in a claim. The word "a" or "an" preceding an element does not exclude the presence of a plurality of such elements.

CLAIMS:

1. Apparatus for performing Orthogonal Polarized Spectral Imaging (OPSI) for imaging objects below the surface of diffuse scattering media, and in particular blood capillaries, in organs, such as the skin of human beings, comprising amongst others at least a light source (1) for providing polarized light, an imaging device (12), a beam splitter (6), an
5 focusing device (7), and means for imaging the object in two different imaging angles.
2. Apparatus according to claim 1, characterized in that the means for imaging the object is formed by two objectives having different imaging angles.
- 10 3. Apparatus according to claim 1, characterized in that the means for imaging the object is formed by a single main objective (7), and a scanning mirror (16), a rotating wedge or 2 shifting wedges for shifting the imaging beam on its path from the polarizing beam splitter (6) to the imaging device (12).
- 15 4. Apparatus according to claim 1, characterized in that separate imaging devices (12) are provided for each image.
5. Apparatus according to claim 4, characterized in that a shutter for alternating transmission of one of the two images is provided.
20
6. Apparatus according to claim 5, characterized in that the shutter is located between the polarizing beam splitter (6) and the imaging device (12).
7. Apparatus according to claim 5, characterized in that the shutter is a rotating
25 aperture shutter.
8. Apparatus according to claim 5, characterized in that the shutter is a liquid crystal cell shutter.

9. Apparatus according to claim 1, characterized in that the two imaging angles differ by 10 to 30 degrees.
10. Apparatus according to claim 1, characterized in that the imaging devices are
5 CCD-cameras.
11. Apparatus according to claim 1, characterized in that the imaging devices are CMOS-sensors.
- 10 12. Apparatus according to claim 1, characterized in further comprising a data processor for determining a position of the object, the position including at least information about the z-axis, which is parallel to the optical axis.
- 15 13. Apparatus according to claim 12, characterized in further comprising a spectroscopic analysis system, with a spectroscopic light source, a spectroscopic light beam positioning device for directing the spectroscopic light beam to the object in dependence of the position of the object determined by the data processor.
- 20 14. A method for detection of objects below the surface of diffuse scattering media, and in particular blood capillaries, in organs, such as the skin of human beings, using Orthogonal Polarized Spectral Imaging (OPSI), comprising the steps of:
- imaging the object in question under at least two different angles, to obtain a shift of position in the imaging plane; and
 - comparing relative shifts of objects in the two images to obtain coordinates of
25 the imaged objects with respect to the organ surface.
15. Method according to claim 14, characterized in that based on the direction of shift it is determined whether the imaged object is above or below the focal plane.
- 30 16. Method according to claim 14, characterized in that based on the size of the shift, the distance between the object and the focal plane is calculated.
17. Method according to claim 1, characterized in that the imaging angle is chosen to be between 10 and 30 degrees.

18. Method according to claim 14, characterized in that for imaging of the object, a single objective (7) is used.

5 19. Method according to claim 18, characterized in that to obtain the at least two images, part of the objective (7) is illuminated with a parallel beam.

20. Method according to claim 18, characterized in that to obtain the at least two images, the whole objective (7) is illuminated under a defined angle.

ABSTRACT:

5 Provided is a method and an apparatus for detection of objects below the surface of diffuse scattering media, and in particular blood capillaries, in organs, such as the skin of human beings, using Orthogonal Polarized Spectral Imaging (OPSI), according to the invention comprising the steps of, imaging the object in question under at least two different angles, to obtain a shift of position in the imaging plane; and subsequently comparing relative shifts of objects in the two images to obtain coordinates of the imaged objects with respect to the organ surface.

Fig. 4

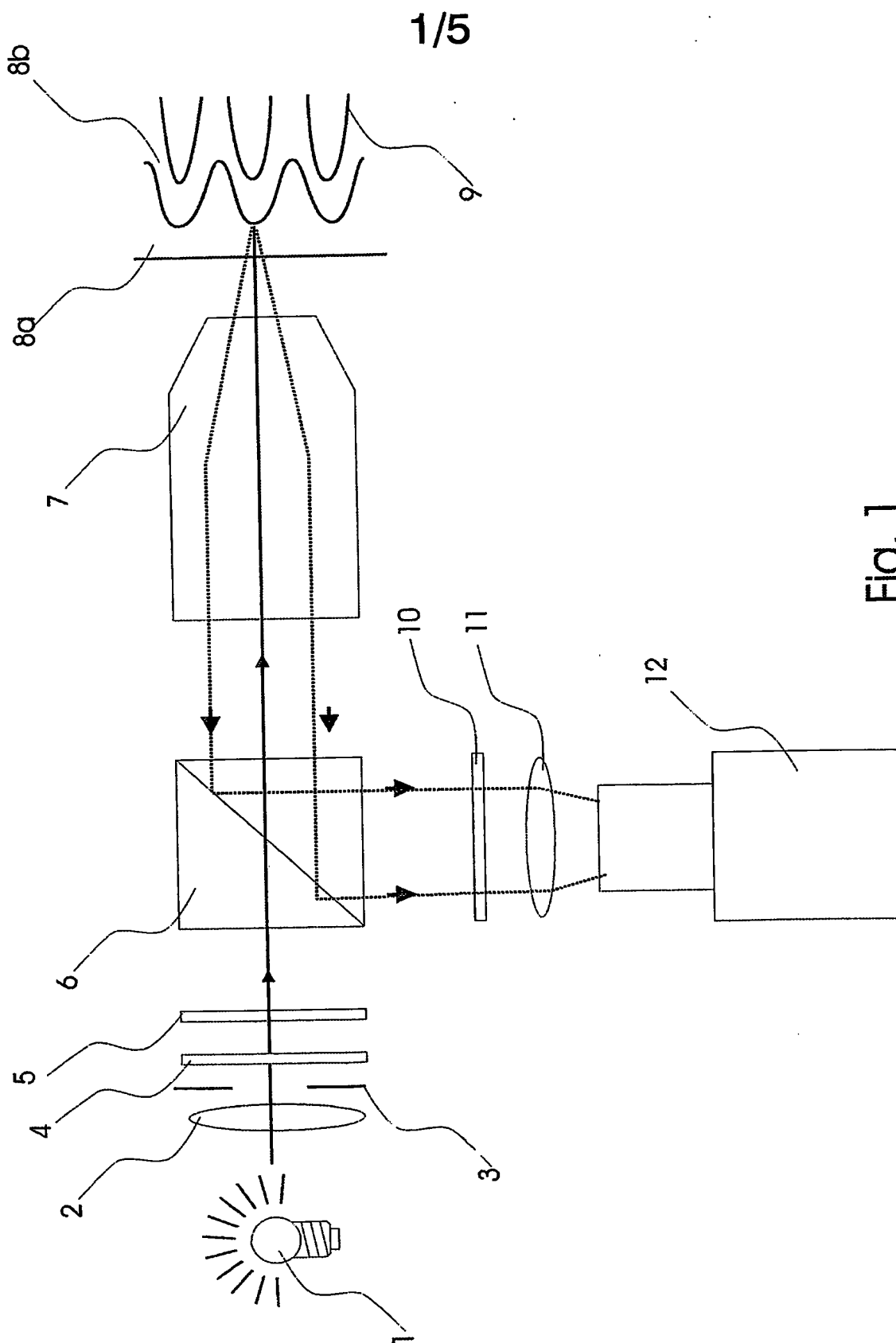
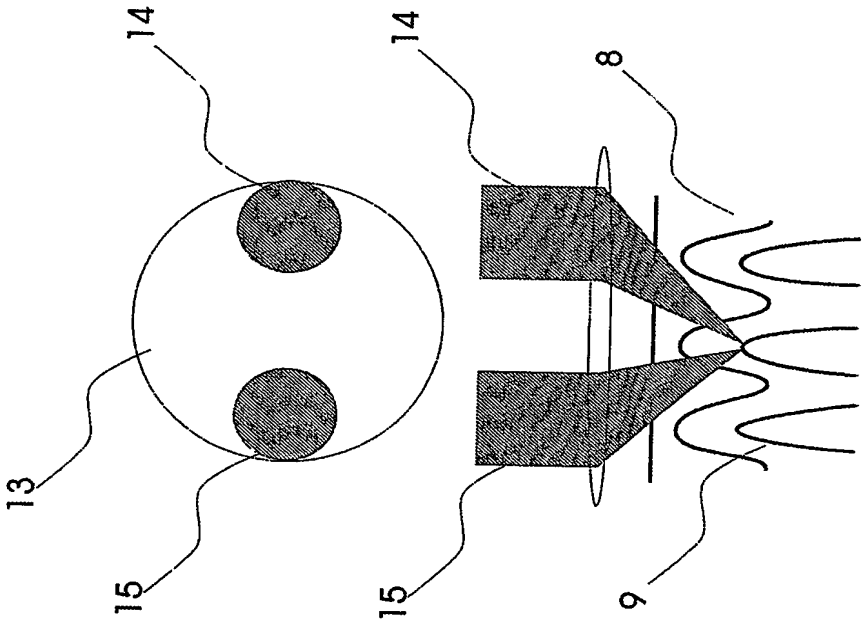


Fig. 2a

Fig. 2b



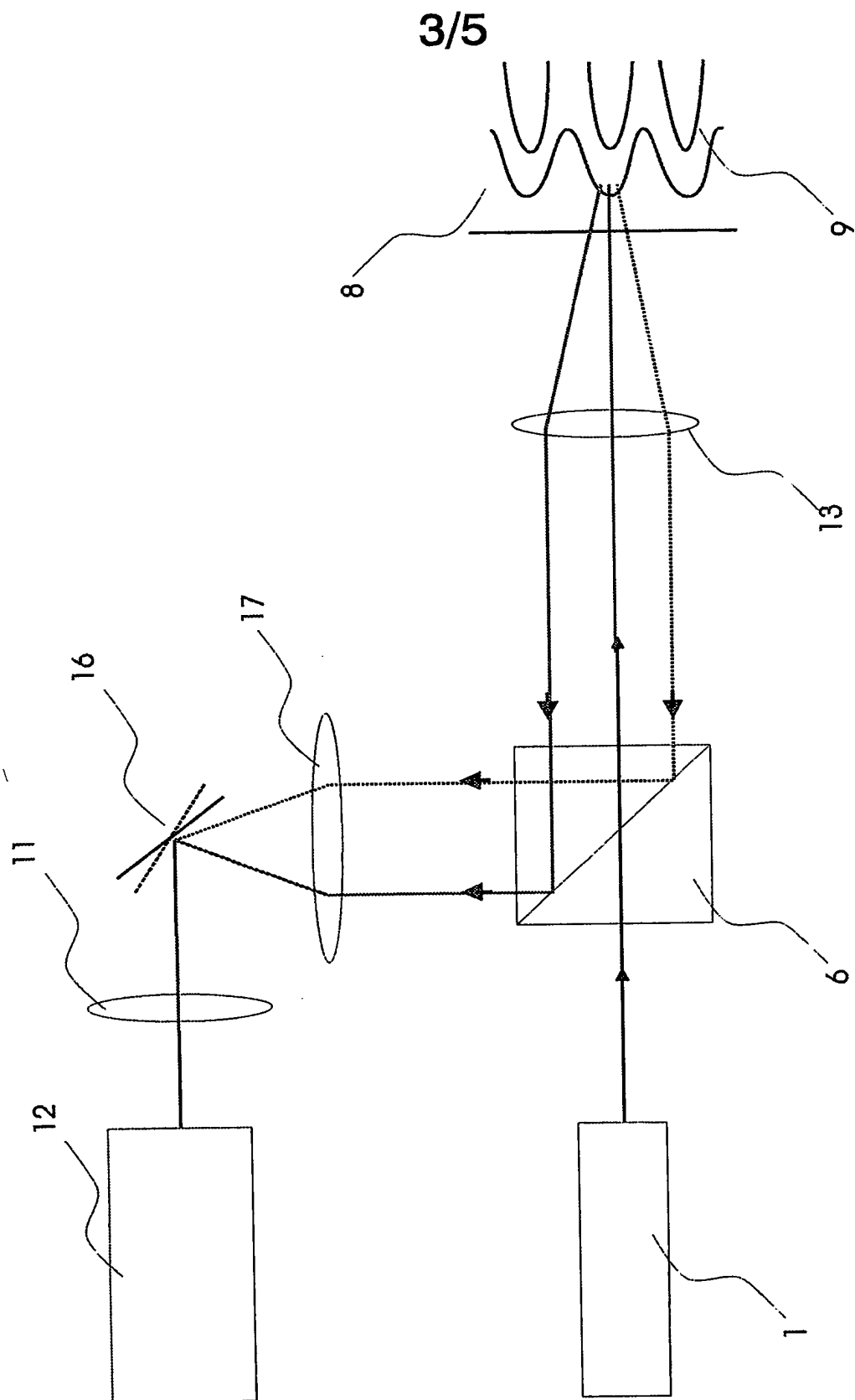


Fig. 3

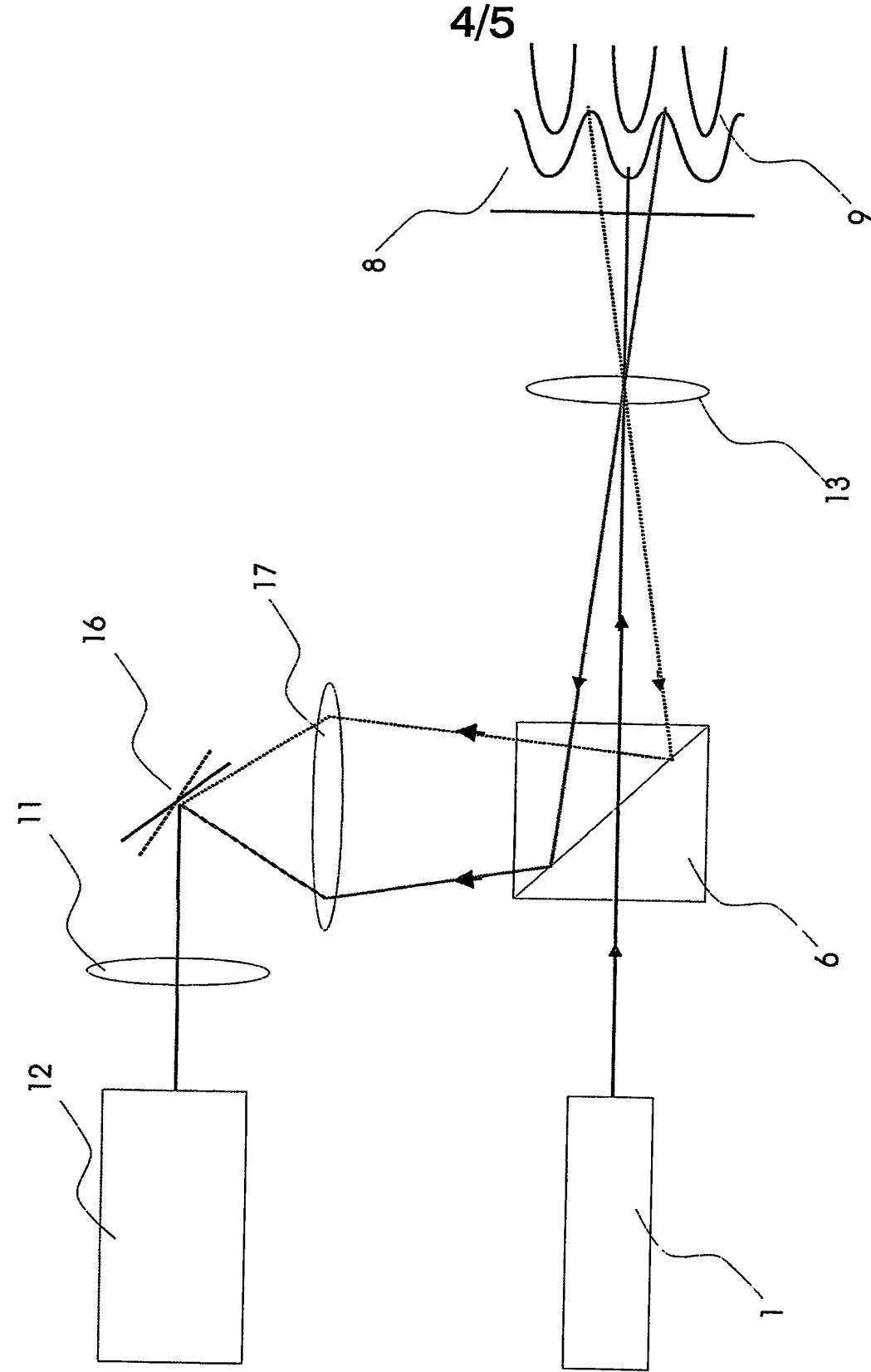


Fig. 4

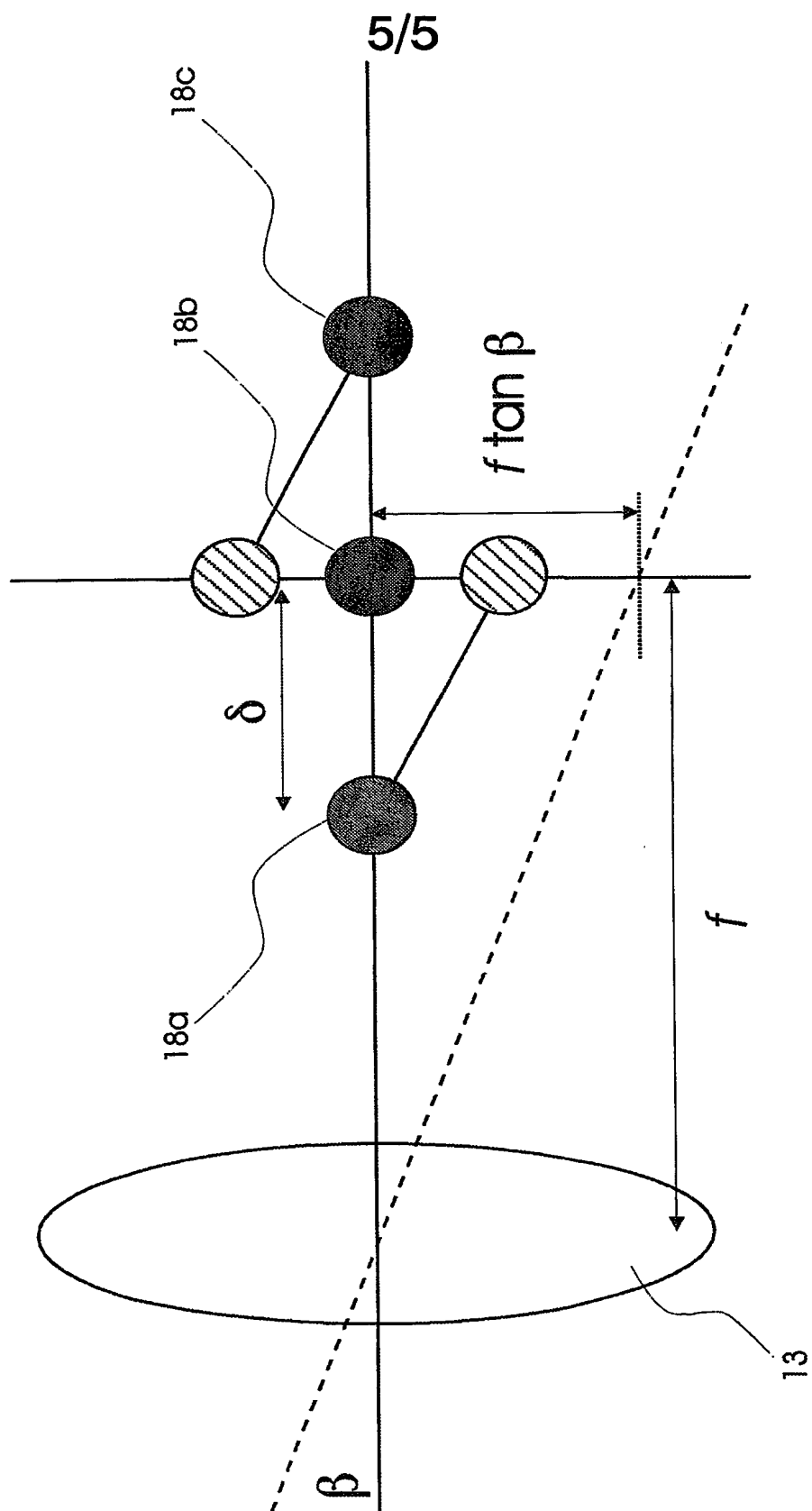


Fig. 5

PCT/IB2004/052862



**This Page is Inserted by IFW Indexing and Scanning
Operations and is not part of the Official Record**

BEST AVAILABLE IMAGES

Defective images within this document are accurate representations of the original documents submitted by the applicant.

Defects in the images include but are not limited to the items checked:

- ☒ BLACK BORDERS
- ☐ IMAGE CUT OFF AT TOP, BOTTOM OR SIDES
- ☐ FADED TEXT OR DRAWING
- ☐ BLURRED OR ILLEGIBLE TEXT OR DRAWING
- ☐ SKEWED/SLANTED IMAGES
- ☒ COLOR OR BLACK AND WHITE PHOTOGRAPHS
- ☐ GRAY SCALE DOCUMENTS
- ☐ LINES OR MARKS ON ORIGINAL DOCUMENT
- ☐ REFERENCE(S) OR EXHIBIT(S) SUBMITTED ARE POOR QUALITY
- ☐ OTHER: _____

IMAGES ARE BEST AVAILABLE COPY.

As rescanning these documents will not correct the image problems checked, please do not report these problems to the IFW Image Problem Mailbox.